

In regard to the deposit, Applicants' attorney certifies, by the signature below, the following:

- - Cell line deposit ATCC HB 11423 will be maintained for 30 years after the date of deposit and will be replaced with living cultures, if such should become destroyed or defective. Further, all restrictions imposed by the depositor on the availability to the public of the cell line deposit as ATCC HB11423 will be removed irrevocably upon the granting of a patent upon the above-identified application.- -

In regard to the rejection under 35 U.S.C. §112, second paragraph, the claims have been amended to refer to the deposited cell line.

Claims 1-8 stand rejected under 35 U.S.C. §103 as unpatentable over Xia or Bombil in view of Queen.

The claims have been amended to facilitate understanding of the invention.

The claims, as amended, are directed to humanized antibodies and the use thereof.

The product claims define over the art of record in that the product claims not only are directed to a humanized form of an antibody which binds to the same epitope as LO CD<sub>2a</sub>, but, in addition, define that certain portions of the human framework are substituted with residues from the donor antibody.

Although the Examiner takes the position that it would have been obvious to humanize LO CD<sub>2a</sub>, such a position is not sufficient to negate the patentability of the claimed invention in that none of the prior art puts one of ordinary skill in the art in possession of the LO CD<sub>2a</sub> antibody.

In particular, the prior art, at best, refers to LO CD<sub>2a</sub>; however, the prior art does not enable one skilled in the art to obtain such an antibody. Xia discloses general methodology for producing monoclonal antibodies, and indicates that one of the antibodies which was obtained is LO CD<sub>2a</sub>. However, Xia does not enable one skilled in the art to practice the methodology and identify and isolate LO CD<sub>2a</sub> antibody or an antibody which binds to the same epitope as LO CD<sub>2a</sub>.

In particular, as the Examiner is no doubt aware, in order to be able to obtain LO CD<sub>2a</sub> antibody, one skilled in the art must have sufficient characteristics which uniquely

identify such antibody so that one skilled in the art could separate and isolate LO CD<sub>2a</sub> antibody from the other antibodies which would be present.

Xia et al. does not provide sufficient information which would enable one skilled in the art to obtain such LO CD<sub>2a</sub> antibody.

Applicant has provided a copy of the declaration filed in co-pending application serial no. 08/472,281, which indicates that the characteristics identified in Xia do not define characteristics which are capable of uniquely identifying LO CD<sub>2a</sub> antibody.

Because one skilled in the art is not enabled by Xia to obtain LO CD<sub>2a</sub> antibody, one skilled in the art is not enabled to produce a humanized form of such antibody.

Although Queen is broadly directed to humanized antibodies and contemplates framework substitutions, such generic disclosure alone or in combination with the other cited art is not sufficient to negate the patentability of the claimed antibodies which are directed to antibodies including a defined framework substitution in combination with defined CDRs.

Although the Examiner has taken a broad position that it would be obvious to humanize an antibody, such position is not sufficient to negate the patentability of the claimed invention wherein the claims are directed to a specific type of humanized antibody, wherein the CDRs are derived from an antibody which is not enabled by the prior art and where there are defined framework substitutions.

In regard to Bombil, such reference also does not enable one skilled in the art to obtain LO CD<sub>2a</sub> antibody. Although the article indicates that LO CD<sub>2a</sub> antibody was used, the reference does not teach one skilled in the art how to obtain such antibody.

Thus, one skilled in the art is not enabled by the prior art to obtain LO CD<sub>2a</sub> antibody and, therefore, is not enabled to obtain a humanized form of such antibody.

Since the claims define the portions of the framework of the humanized antibody which include residues obtained from the antibody from which the CDRs are obtained, the claims further define over the art of record in that none of the art of record specifically suggests substituting residues at the defined positions when the CDRs are obtained from an antibody which binds to the same epitope as LO CD<sub>2a</sub>.

Thus, even if the LO CD<sub>2a</sub> is enabled by the cited prior art (which it is not), the claims which are directed to antibodies with defined framework substitutions in combination with certain CDRs are patentable in that the claimed prior art alone or in combination does not disclose the portions of the donor antibody which should be substituted in the framework when using the defined CDRs.

As a result, all of the product claims are patentable over the prior art.

Reconsideration and withdrawal of the rejection are requested.

In regard to the method claims, such method claims are patentable over the prior art for the reason, among others, that the prior art does not place those skilled in the art in possession of the compounds used in the claimed process.

Even if such were not the case, the prior art does not provide any reasonable expectation that the claimed antibodies could be successfully used in a human. In fact, the prior art, as a whole, suggests that CD2 antibodies would not be successful.

In this respect, Thurlow et al. (Transplantation, vol. 36, pgs. 293-97), copy attached, reports that an attempt to use a CD2 monoclonal antibody in a human was not successful.

Giorgi (Transplantation Proceedings, vol. 15), which is of record, reports that another CD2 antibody was not successful in primate studies.

Thus, there is nothing in the prior art which would lead one to expect that the claimed antibodies could be used in treating patients.

The Examiner's attention is drawn to pages 40-43 of the Specification, which provides human data. It is noted that the human data shows successful treatment after onset of rejection; that is, the treatment can reverse rejection.

This should be contrasted with the indication in the prior art that CD2 antibodies, if effective at all, would be effective only if administered immediately after T-cell priming (Guckel, pg. 964, par. bridging cols. 1 and 2).

As the Examiner is no doubt aware, in treating rejection or other T-cell mediated responses, it is virtually impossible to treat within 24 hours of antigen "priming."

Thus, the ability to treat patients successfully in accordance with the invention would not be expected from the prior art. In fact, the prior art suggests that CD2 antibodies would not be suitable for the treatment of patients.

As indicated in the Declaration of Mary White-Scharf filed in co-pending application serial no. 08/472,281 (copy enclosed), the LO CD<sub>2a</sub> antibody binds to a unique epitope.

Because it is well-known in the art that antibodies function through their epitopes, the data indicates that the antibodies of the present invention may be employed for treating of patients.

Because the prior art does not suggest the antibodies of the present invention, and since the prior art, in fact, would lead one skilled in the art to expect that CD2 antibodies could not be employed for treating of patients, the method claims are deemed to be patentable over the art of record.

Reconsideration and withdrawal of the rejection is requested.

In regard to the provisional double-patenting rejection, the claimed subject matter is patentable over the noted co-pending applications in that the present application is directed to a humanized antibody in which there is a framework substitution at defined positions. Although the allowed claims in application 08/477,877 encompass a humanized form of LO CD<sub>2a</sub>, claims which are directed to a humanized form of LO CD<sub>2a</sub> wherein there is substitution of donor amino acid residues at specified positions is patentably distinguishable from the claimed subject matter. As a result, a terminal disclaimer is not required.

In regard to the potential rejection under 35 U.S.C. §102(f) or (g), the humanized form of the antibody, defined in the present application, patentably defines over the noted co-pending applications by defining donor residues which are substituted in the framework.

Although the LO CD<sub>2a</sub> antibody, including humanized and chimeric forms thereof was invented by the applicants of the noted co-pending applications, the present application, which includes additional inventors, claims a patentably distinguishable

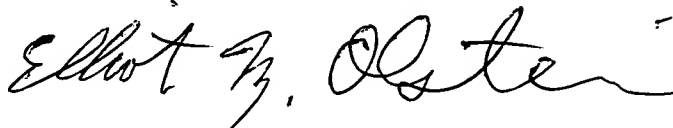
invention by defining certain framework residues which are substituted from the donor antibody into the human framework.

The substitution of such defined residues is not rendered obvious by the prior work of the named inventors of the noted co-pending applications.

Although the disclosures of the co-pending applications are identical, the subject matter with respect to defined substitutions in the human framework was the joint invention of the applicants of the present application. Since the co-pending applications do not specifically claim the defined substitutions and since the defined substitution is a joint invention of the inventors of the present application, which is patentably distinguishable from LO CD<sub>2a</sub> antibody and a generic invention of a humanized form thereof, there is no conflict between the claims of the present application and those of the noted co-pending applications.

This application is considered to be in condition for allowance, and an early notice to this effect is solicited.

Respectfully submitted,



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